Evaluation of tolerability of enteric-coated mycophenolate sodium *versus* mycophenolate mofetil in *de novo* renal transplantation

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ABSTRACT

Introduction: Mycophenolate mofetil (MMF), pro-drug mycophenolic acid (MPA) is an immunosuppressive effective in the prophylaxis of acute rejection, but associated with gastrointestinal adverse events. Mycophenolate sodium (MPS) with enteric coating was developed with intention of reducing such gastrointestinal adverse events associated with MPA. **Objective:** To evaluate the tolerability of EC-MPS and MMF in renal transplant recipients. **Methods:** Retrospective, multicenter study, included 1380 patients who underwent a transplant between 07/01/2004 and 31/07/2007 in 18 Brazilian centers. **Results:** 1380 patients enrolled, 702 received EC-MPS and 678 received MMF. The average age of patients was 42.3 years, 60% were male and 62.5% of Caucasian ethnicity. The incidence of events evaluated in the composite endpoint of efficacy was not different between groups at the end of 24 months follow-up (22.9% for EC-MPS to MMF *versus* 19.9%, p = 0.203). Patients treated with EC-MPS had a higher incidence of gastrointestinal adverse events compared to those treated with MMF (57.7% *vs.* 52.5%), but there was no statistical difference between groups. Viral infections were more frequent in the EC-MPS group (38.2%) compared with MMF (32.6%). There was no difference in mean tolerated dose after the first (1187 ± 344 *vs.* 1209 ± 426 mg, p = 0.294) and second year (1172.3 ± 347 mg *vs.* 1197.4 ± 430.6 mg, p = 0.241) after transplantation. **Conclusion:** There was no statistical difference in the incidence of acute rejection, delayed graft function and gastrointestinal events among treatments. The average tolerated dose of MPA was similar between groups; however, patients treated with MMF underwent more dose reductions and discontinuations of treatment.

Keywords: graft rejection; immunosuppression; kidney transplantation.

INTRODUCTION

Mycophenolate mofetil (MMF, Cellcept®, Roche, Nutley, NJ) is an esterified prodrug of mycophenolic acid (MPA) that inhibits inosine monophosphate dehydrogenase (IMPDH), an enzyme involved in the de novo synthesis of guanosine nucleotides. Differently from other cell lineages, T and B cells rely on this pathway to synthesize purines, compounds with a prominent role in cell proliferation.[1]

MMF was introduced in the United States in 1995, while in Brazil the drug has been available since 1998. The prescription of MMF combined with calcineurin inhibitors has been associated with excellent short and long-term outcomes among kidney transplant patients, with improved graft survival and decreased occurrence of acute rejection.[2]

However, the adverse gastrointestinal events correlated with the use of MPA may negatively affect patient quality-of-life and compliance to treatment. In clinical settings, approximately 50% of the patients have the

dosage of their medication reduced or treatment with MMF suspended or even discontinued, thus compromising the efficacy of the therapy.[3,4]

Enteric-coated mycophenolate sodium (EC-MPS, Myfortic®, Novartis Pharma AG; East Hanover, NJ), prescribed in the prophylactic care of kidney transplant patients at risk for acute rejection, was developed to mitigate the adverse gastrointestinal events associated with the use of MPA. The enteric-coated drug allows MPA to be released only in the duodenum, within an area with a pH of approximately 5, thus avoiding undesired gastrointestinal events.[1]

The therapeutic equivalence of MMF and MPS was assessed in a phase III multicenter randomized double blind parallel-group trial with 423 de novo kidney transplant recipients. Treatment failure (defined as acute rejection confirmed by biopsy, graft loss, death, or patient loss during follow-up six months after transplantation) was similar between therapies (25.8% *vs.* 26.2% for EC-MPS and MMF, respectively). Fewer patients on EC-MPS (15%) required dose reductions when compared to individuals on MMF (19.5%), but no statistically significant differences were observed in the incidence of adverse gastrointestinal events.[5]

Nonetheless, retrospective studies looking into the tolerability of EC-MPS *vs.* MMF reported fewer adverse events and less need to reduce drug dosage in patients treated with EC-MPS.[6,7]

Favorable outcomes for EC-MPS have also been reported in studies enrolling patients converted from MMF to EC-MPS, with significant reductions in adverse gastrointestinal events and improvements in quality-of-life.[8,9]

The myriad conflicting findings reported in the literature drove the authors of this study to retrospectively review the tolerability of EC-MPS and MMF in kidney transplant patients treated in renal care centers in Brazil.

Methods

This retrospective multicenter study enrolled 1,380 de novo kidney transplant patients submitted to transplantation between July 1, 2004 and July 31, 2007, in 18 centers in Brazil. The ethics committees of each of the involved centers approved the study.

Study population

The study population included living and deceased-donor adult kidney transplant recipients started on primary immunosuppression with MMF or EC-MPS plus a calcineurin inhibitor and steroids. Kidney-pancreas transplant patients, individuals offered transplants of other solid organs, patients on single-drug therapy with MPA or combined with proliferation signal inhibitors (sirolimus or everolimus), and grafts lost due to technical reasons or for failing to present primary function were excluded.

Immunosuppression

The patients included in the study were given initial immunosuppression with MMF or EC-MPS combined with cyclosporine or tacrolimus and steroids, with or without induction therapy based on monoclonal or polyclonal antibodies. The criteria used to prescribe induction therapy, define immunosuppressant dosages, and offer concurrent prophylactic care were established at each individual center. The same applied to the tapering down or discontinuation of MPA drug therapy.

Parameters and outcomes considered

Efficacy - or failure - was assessed through a composite endpoint including acute rejection confirmed or not by biopsy, graft loss, and death.

The assessed safety parameters included the incidence of adverse gastrointestinal events, renal function, time of hospitalization, and episodes of infection.

Tolerability was analyzed based on information concerning the reduction (reductions on the total daily medication dosage) or discontinuation (MPA therapy discontinuation) of MMF or EC-MPS therapy.

Patient data were gathered retrospectively from the date of transplant until 12 months or 24 months after transplantation in the case of transplants performed between 2004 and 2005.

Statistical analysis

Student's *t*-test was used to compare the mean values of the normally distributed homogeneous quantitative variables captured for each treatment group. Otherwise, quantitative variables were analyzed through the Mann-Whitney U test. The chi-square test or Fisher's exact test were used in the analysis of qualitative data (dosage reduction or therapy discontinuation, adverse events, and infection). The cumulative MPA reduction/discontinuation-free survival curve (*Kaplan-Meier* curve) was analyzed using the log-rank test. All statistical tests were two-sided with a significance level of $p < 0.05$.

Results

Demographics and clinical characteristics

The final cohort consisted of 1,380 patients, 702 in the EC-MPS and 678 in the MMF group. Table 1 describes the main clinical and demographic characteristics of the patients. The patients' mean age was 42.3 (± 12.3) years; 60% were males; and 62.5%, were Caucasians. Glomerulonephritis was the etiology of the baseline disease in approximately 20% of the patients, whereas in 21.5% the cause of disease was unknown. The comparison of the two treatment groups revealed that a greater number of patients on EC-MPS received kidneys from deceased donors or donors with expanded criteria. Approximately 50% of the patients were given induction therapy, with interleukin-2 receptor antagonists (32.2%) on the top of the list. No statistically significant differences were seen between the groups on the use of calcineurin inhibitors; 73% of the patients were on tacrolimus and 27% on cyclosporine (Table 2).

Efficacy

The incidence of the events included in the efficacy composite endpoint was not statistically different between the groups after 24 months of follow-up (22.9% for EC-MPS *vs.* 19.9% for MMF, $p = 0.203$). No differences were found in the incidence of acute rejection, graft loss, or death between the groups (Table 3).

Safety

Although the patients treated with EC-MPS had a higher incidence of adverse gastrointestinal events than the individuals treated with MMF (57.7% *vs.* 52.5%), no statistically significant differences were found between the groups. The most frequently reported events were diarrhea (45.2% *vs.* 37.4%), upper abdominal pain (10.9% *vs.* 10.3%), vomiting (8.3% *vs.* 10.1%), abdominal pain (8.1% *vs.* 8.7%), and nausea (4.8% *vs.* 8.7%) for the MPS and MMF groups, respectively. This outcome was observed only for general and moderate to severe adverse gastrointestinal events.

The incidence of delayed graft function (DGF) was significantly higher in the EC-MPS group (62% *vs.* 51%; $p = 0.007$).

The groups did not present significant differences in renal function in the time period covered by the study. The mean glomerular filtration rates (GFR) of the individuals in the EC-MPS and MMF groups 24 months after transplantation were 60.6 ± 24.8 ml/min and 59.9 ± 20.7 ml/min ($p = 0.311$), respectively. The same was seen for proteinuria.

The individuals in the EC-MPS group had longer mean times of post-transplant hospitalization (22.4 ± 31.7 days) than the patients treated with MMF (18.6 ± 34.9 days), $p = 0.035$.

Infection was also more common in the EC-MPS than in the MMF group (69.0% *vs.* 54.8%), with urinary tract and cytomegalovirus infections ranking as the most frequent manifestations. A subanalysis considering only viral infections revealed incidences of 38.2% and 32.6% in the groups given EC-MPS and MMF, respectively ($p = 0.051$).

Tolerability

The comparison of equimolar doses of the two drugs (360 mg of MPS equivalent to 500 mg of MMF) failed to reveal differences in the mean tolerated doses 12 months (1187 ± 344 mg *vs.* 1209 ± 426 mg, $p = 0.294$) and 24 months (1172.3 ± 347 mg *vs.* 1197.4 ± 430.6 mg, $p = 0.241$) after transplantation.

Table 1 Demographics

Parameters	Total (N = 1380)	EC- MPS (N = 702)	MMF (N = 678)
Age, years	42.3 ± 12.3	43.0 ± 12.4	41.7 ± 12.2
Gender (%)			
Male	55.9	58.8	52.8
Female*	44.1	41.2	47.2
Ethnicity (%)			
Caucasian	62.5	61.4	63.5
African descent	16.0	18.7	13.3
Asian	0.5	0.3	0.8
Other	16.5	16.1	16.9
Etiology of kidney disease (%)			
Diabetes mellitus	6.7	6.7	6.7
Glomerulonephritis	20.4	16.3	24.7
Unknown	21.5	24.4	18.5
Other	51.3	52.6	50.0
Time on dialysis, months	44.6 ± 40.5	46.1 ± 39.2	43.0 ± 41.9
Re-transplant (%)	5.3	6.1	4.7
Deceased donor (%)*	54.5	62.3	46.3
Expanded criteria donor (%)*	13.9	16.6	9.7
Time on cold ischemia, hours	20.9 ± 6.6	20.5 ± 6.6	21.3 ± 6.6

* $p < 0.05$.

Table 2 Initial immunosuppression

Induction therapy and immunosuppressive therapy	EC-MPS	MMF
Induction therapy (%)	34.3	30
IL2-Ra	0.09	1.2
OKT3	17.1	12.2
Thymoglobulin	47.7	56.6
No induction therapy		
Calcineurin inhibitors (%)	25.3	27.9
Cyclosporine	74.5	71.6
Tacrolimus		
Mycophenolate, g	1350.1 ± 240.5	1927.4 ± 299.0
Prednisone (%)	99.7	99.4

Table 3 Efficacy endpoints

Endpoints (%)	EC-MPS	MMF
Delayed graft function*	62	51
Acute rejection, treated	49.4	50.5
Acute rejection, confirmed by biopsy	19.1	16.7
Graft loss	3.8	2.4
Death	2.6	2.1

* $p < 0.005$.

The need to reduce dosages and discontinue treatment was greater in the group given MMF both twelve (76% *vs.* 65%, $p < 0.001$) and 24 months after transplantation (79% *vs.* 84%, $p = 0.015$), Table 4.

However, in both groups the main reason for treatment discontinuation was not medical, but administrative, as the medication offered free of charge to the patients was changed by the State Secretary of Health. In some States, MMF was replaced with EC-MPS, while in others the opposite occurred. These changes accounted for 46% of treatment discontinuations in the MMF group and 24% in the EC-MPS group. The second most common reason for discontinuation was adverse gastrointestinal events (18% *vs.* 21%), followed by unknown or unreported factors (14% *vs.* 17%) in the MMF and EC-MPS groups, respectively.

Figures 1A and 1B show the Kaplan-Meier curves for MPA reduction and discontinuation rates 12 and 24 months after transplantation, respectively.

Discussion

Dose reductions, treatment discontinuation, and poor compliance of patients treated with MPA as a

Table 4 Mycophenolate dosage reduction and discontinuation

	EC-MPS	MMF
12 months*	64.7	75.9
24 months*	78.8	84.1

* $p < 0.05$.

consequence of adverse gastrointestinal events have been described as risk factors for acute rejection[3,4] and graft loss,[4] in addition to increased short-term treatment costs.[10,11]

The similar mean tolerated dosages of MPA found 12 and 24 months after transplantation and the significant number of patients who had their treatments changed for non-medical reasons did not allow the identification of differences in tolerability in this retrospective study.

The patients treated with EC-MPS had non-statistically higher incidences of adverse gastrointestinal events and viral infection. Some of the clinical and demographic parameters described for these patients may have affected their medical outcomes, as they have been associated with greater risk: longer time on dialysis, greater number of re-transplants, and greater number of expanded criteria donors. The higher incidence of DGF and longer hospitalization times added to the risk expected for this group of patients.

DGF may have also contributed to the higher incidence of adverse events observed in the patients on EC-MPS, once unsatisfactory renal function may affect the exposure to MPA due to reduced MPAG (mycophenolic acid glucuronide, the main MPA metabolite) excretion.[12] Additionally, elevated blood urea impairs the binding of MPA to albumin, thus increasing the concentration of free MPA.[13] Therefore, patients with DGF are more exposed to MPA and increased related toxicity.[1]

In this study, the patients treated with EC-MPS were given more induction therapy with antibodies than the individuals prescribed MMF. Induction therapy has been associated with increased risk for viral infection, a finding also observed among patients in this group.

Cohort studies based on large databases have associated reductions in MMF doses with increased risk of acute rejection and graft loss.[5,6] Recently, a retrospective study with 1,709 kidney transplant recipients treated with MMF (1,111) or EC-MPS (598) revealed that, despite the similarities between the groups in terms of graft survival and kidney function, the incidence of biopsy-confirmed acute rejection two years after transplantation was significantly higher in the cohort treated with MMF (30.2% *vs.* 21.9%).[6] A retrospective study enrolling 379 patients reported lower incidences of biopsy-confirmed acute rejection among patients treated with EC-MPS (14%) *versus* MMF (23,1%); however, no significant differences were found in the incidence of adverse gastrointestinal events seen in the groups.[14] Another study compiled the results of a number of prospective studies and described lower levels of treatment failure for kidney transplant recipients given EC-MPS (23.9%) than for patients treated with MMF (28.9%).[5]

Unlike other published studies, our series failed to elicit significant differences in the incidence of biopsy-confirmed acute rejection, despite the higher immune risk of patients treated with EC-MPA.

The limitations of this study are relevant and must be considered. In addition to the retrospective nature of the analysis, the changes of a non-medical nature made to the treatment offered to the patients have directly impacted the outcomes described in it. Information on factors such as the reason why drug dosage was reduced were frequently missing from patient records, thus limiting the authors' ability to compare between groups. Another limitation was the distribution of patients within the studied period (2004 to 2009). Most patients on EC-MPS were followed only for the last two years of the study. In this case, the medical community had to go through a learning curve with MMF and the skills acquired in the process may have facilitated the treatment of patients prescribed EC-MPS.

Conclusion

The mean tolerated dosage of MPA was similar for both groups. Despite the demographic and clinical parameters associated with increased risk observed in the EC-MPS group, no statistically significant differences were found between the groups for incidence of acute rejection, DGF, or adverse gastrointestinal events.

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